[Frontiers In Bioscience, Elite, 10, 1-14, January 1, 2018]

Centchroman: A safe reversible postcoital contraceptive with curative and prophylactic activity in many disorders

Ved P. Kamboj[1], Suprabhat Ray[1], Nitya Anand[1]

[1]Central Drug Research Institute, Lucknow, India

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1. ABSTRACT

Centchroman (INN: Ormeloxifene), a reversible post-coital/weekly oral contraceptive (half-life of about 168 hours), designed and developed at CDRI, Lucknow is the only non-steroidal oral contraceptive in clinical use in the world today. Synthesized in 1967 and completing pre-clinical and clinical studies in 1989, this drug was approved for marketing in 1991, social marketing in 1995 and NFPW in April 2016. It acts by preventing implantation of blastocyst in endometrium. It is the only contraceptive which neither suppresses ovulation nor interferes with the hypothalamic-pituitary-ovarian axis. It has high level of safety and is virtually free from side effects except for a delay in about 8% menstrual cycles which is not confined to any women/cycle. Besides contraception, this SERM is also clinically useful in the management of DUB, mastalgia and fibroadenoma and has promising therapeutic efficacy in a variety of cancers including breast cancer. Due to estrogenic activity, this drug also has anti-osteoporotic and cardioprotective activity. Thus, Centchroman is likely to show other curative and prophylactic activity in a wide range of other disorders.

2. INTRODUCTION

Population Control and Family Planning have been of deep interest to the Government of India almost since independence in 1947. The first structured family planning programme was launched by the Ministry of Health in 1952. The ministry in its strategy and plan for family planning called upon Central Drug Research Institute, Lucknow (CDRI) in 1960 to develop suitable contraceptives for family planning. In 1960 in USA, the steroidal oral contraceptive pill, Enovid, a combination of a progestagen (norethynodrel) and estrogen was approved by US-FDA with a few riders, due to some worrisome side effects such as nausea, dizziness, stomach pain, weight gain, menstrual disorders, etc. Further the steroidal oral pills prevented pregnancy by suppressing ovulation, thus disturbing the hypothalamus-pituitary-ovarian axis. CDRI was very conscious of the fact that the contraceptives will be used by young women who are in the prime of their youth, and should therefore not be made to use a contraceptive which would in any way disturb their normal reproductive physiology/function. So, CDRI ruled out to work on contraceptives that would disturb ovulation. Further by now it was quite well established that the side effects of nausea, weight gain etc. were the result of the steroidal character of the contraceptives. The CDRI therefore decided to focus its emphasis on exploring non-steroidal antiestrogens as contraceptives. During this period the classical paper of Lerner *et al* (1958) was published describing the first non-steroidal estrogen antagonist, MER-25 (1; Figure 1), which antagonized the activity of both endogenous and exogenous estrogens (both steroidal and non-steroidal) but were not anti-ovulatory and prevented pregnancy in rats when given post-coitally. This was a big event in antiestrogens development and new analogues started appearing soon. It was shown that some of these analogues though prevented pregnancy in rats and were pro-ovulatory in sub-fertile women (2). CDRI from the beginning focused attention on the development of post-coital contraceptives (no need to take daily) which would not inhibit ovulation or disturb the hypothalamus-pituitary-ovarian axis and should be free from the side-effects of steroidal contraceptives. The lead provided by MER-25 seemed to meet these requirements, and the Institute chose to design and develop non-steroidal post-coital contraceptives based on the MER-25 lead. The estrogen receptor had not yet been isolated and characterized, and thus the ligand-receptor interaction was mainly hypothetical. Based on the structure-activity parameters the ligands gave the vision of a triphenyl-ethylene or ethane scaffold with interactive functional groups on the periphery interacting with some receptor sites. It was thus decided to design such a scaffold with a carbo or heterocyclic structure to give it a well-defined geometry such as shown in Figure 1.

The chemistry efforts centered on the synthesis of diarylbenzo- and naphtha-furans, indoles, diaryl-benzo-cycloalkanes (5,6 & 7 membered) and 3,4-diarl-coumarines, -chromenes and -chromans. All the compounds were put through appropriate antifertility protocols. Based on extensive structure-activity-relationship (SAR), lead optimization and safety studies *trans*-1-[2-{4-(7-methoxy-2,2-dimethyl-3-phenyl-3,4-dihydro-2-H-1-benzopyran-yl)-phenoxy}-ethyl] pyrrolidine was selected for detailed development. It was named **Centchroman**, a chroman derivative developed by CDRI, and was allotted the INN: **Ormeloxifene** by WHO. At CDRI it is also referred to as 67/20, as it is the 20th compound synthesized in the year 1967 (3).

3. CENTCHROMAN (ORMELOXIFENE)

Centchroman is a mixture of d- and l-isomers. Both the isomers have been isolated and show

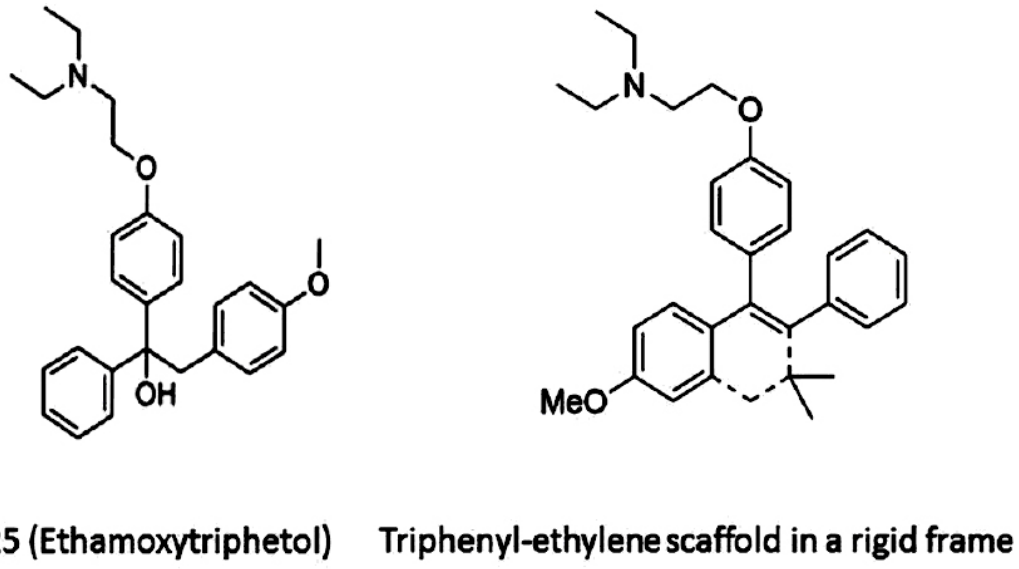


Figure 1. MER-25 and design of the triphenylethylene/ethane scaffold in a rigid frame.

post-coital contraceptive activity in rat; l-isomer is more active but d-isomer does not interfere with l-isomer's antifertility activity (4). On pharmacoeconomic considerations, it was decided to develop the racemic compound, Centchroman (ormeloxifene) as a contraceptive to maintain affordability. It is stable at room temperature for more than three years. Centchroman (ormeloxifene) and its l-isomer (levormeloxifene) were licensed to Zymogenetics, USA (a unit of Novo Nordisc, Sweden) in 1993 for new uses namely osteoporosis, restenosis and other estrogen related disorders.

The detailed drug development has been carried out as per schedule 'Y' regulatory requirements of the Drugs & Cosmetics Act of India using well laid down SOPs.

4. PRE-CLINICAL DEVELOPMENT

4.1. Reproductive Biology

4.1.1. Contraceptive efficacy

Centchroman prevents pregnancy in different rodent species, dogs and rhesus monkeys when given as a single dose (1.25 mg/kg) within 24 hours of coitus; it was equally effective when given for five days (0.25 mg/kg) beginning on day 1 of coitus to rodents. The compound does not induce abortion or resorption in rodents when given immediately after implantation or thereafter. The pups were born at term and presented normal development milestones (5).

Centchroman does not disturb estrous cycle, mating behaviour, ovulation, gamete transport and fertilization as normal corpora lutea are seen in the mated rats. Blastocysts recovered from these mated rats implant normally after progesterone-priming in delayed implantation model or foster mothers and result in normal offsprings. Centchroman given post-coitus induces about 12 hours stimulus in the rate of tubal transport and cleavage of pre-implantation embryos, blastocyst formation and zona shedding. However, blastocysts in delayed implantation model are normal as they have been shown to implant after progesterone administration. The main effect of Centchroman appears to be on endometrial receptivity. Thus Centchroman appears to exert its contraceptive action by producing asynchrony between blastocyst movement and endometrial receptivity to blastocyst resulting in inhibition of implantation in the uterus (6–8).

4.1.2. Hormonal profile

Centchroman shows weak estrogenic and potent antiestrogenic activity. It lacks progestational activity but shows antipogestational effect in a number of bioassays, but does not inhibit progesterone binding to its receptor or interfere with plasma progesterone or alter the progesterone effects in rat uterus. Centchroman has no effect on gonadotrophins content in the pituitary or in plasma and does not inhibit ovulation, mating behavior or disturb hypothalamus-pituitary-ovarian axis in rat. It has no effect on adrenal and thyroid functions (6–8).

4.2. Pharmacokinetics

4.2.1. In Animals

Centchroman administered per oral to rats increased its plasma concentration up to 12 hours and then gradually declined to the single peak

before reaching undetectable levels by 7 days. The metabolite 7-desmethylcentchroman was detected in most of the tissues after one hour and in plasma after two hours but was not seen by 96 hours. The half-life of Centchroman in plasma of female rats is 24.1 hours and that of its metabolite is 36.6 hours; the mean residence of both in uterus is about 120 hours.

The total radioactivity in all tissues after administration of labeled Centchroman to monkeys reached maximum levels at 4 hours and was undetectable in blood by 192 hours. It does not compete with steroid hormones or estrogen agonists/antagonists. Thus it is unlikely to displace steroids from their steroid binding plasma proteins (7–9).

4.2.2. In Normal Women

A single oral dose of 30 mg or 60 mg Centchroman was administered to two groups of healthy women volunteers of reproductive age. The serum maxima at 30 mg dose is seen at 5 hours with terminal half-life of about 165 hours while with 60 mg dose the serum maxima is attained at 4 hours with terminal disposition half-life of about 168 hours. Pertinently, there is no difference in the rate of absorption, distribution or elimination at the two doses; however, the Cmax and AUC appear to be dose dependent. Serum concentration-time data can be best described by a two compartment open model with first order absorption and elimination constants (7,8,10).

4.2.3. In Lactating Women

Centchroman at 30 mg single oral dose was given to two batches of 3 and 4 healthy lactating women. Single time-point milk/serum maxima reveal that Centchroman crosses blood: milk barrier and is excreted in milk. The ratio between serum concentration in mother and that in milk at 4 hours is 0.002. This means that only about 2.5% of mother's dose is excreted in milk. A serum maximum was seen at 6 hours with elimination half-life at about 160 hours while that in milk occurred at 8.5 hours with elimination half-life of about 240 hours. Milk/serum AUC ratio of Centchroman is 0.86±0.63. The weekly milk intake by the child is normally assumed to be 1.05 L/kg body weight and with 100% absorption, average amount of Centchroman excreted in breast milk likely to be taken by the baby weighing 9.5 kg is estimated to be about 50 µg/kg/week or say about 7% per week of maternal dose and as per accepted criteria is unlikely to be of much physiological consequence to suckling babies (7,8,10). This has been confirmed in clinical trials as the children delivered by method and user failures show normal milestones up to five years and in some cases even up to 11 years (7,8,11).

4.3. Regulatory Safety studies

Centchroman is devoid of any effect on gross behavior, or central nervous system except for mild anorexigenic activity at a very high dose, non-specific spasmolytic activity in isolated guinea pig ileum and anti-inflammatory activity comparable to that of phenylbutazone at much higher doses in acute and chronic tests of inflammation and arthritis and an incomplete alpha-adrenergic blockade. It exerts its anti-inflammatory effect directly on tissues and is not mediated via pituitary-adrenal axis or its weak estrogenic activity. It is unlikely to cause gastric irritation because of lower ulcerogenic index than phenylbutazone. It has not caused hyperaggregability of platelets in women who have used 30 mg dose of Centchroman for one year or more which is probably due to inhibition of platelet cyclooxygenase. Centchroman even at very high doses has no effect on vascular cyclooxygenase in rats suggesting thereby its sparing effect and which may prove beneficial against risk of thrombotic episodes by shift of balance towards more beneficial antiaggregatory PGI_2. Conjoint administration of non-steroidal anti-inflammatory drug, Ibuprofen, or anti-tuberculosis drug, Rifampicin with Centchroman during the pre-implantation period has no effect on contraceptive efficacy of Centchroman or its terminal half-life (7,8,12,13).

Centchroman is well tolerated and has an excellent therapeutic index (> 1800). No toxicity has been observed in haematology, clinical chemistry or histopathology (of all the organs) parameters when given at many times the contraceptive dose for 3, 6 and12 months to rats and rhesus monkeys. Administration of compound during the entire period of organogenesis in animals does not affect the embryos during the post-natal growth period. All the development milestones and fertility of offspring remained normal. Centchroman has no mutagenicity and genotoxicity. It has no carcinogenic effect when given for entire life-term at much higher doses to rodents (7,8,14).

5. CLINICAL USE DEVELOPMENT

5.1. Clinical pharmacology

Centchroman was given orally, in double blind non-cross over study, to healthy male and female volunteers at doses ranging from 5 mg to 320 mg, single dose per volunteer beginning with the lowest dose. The multiple dose study, double blind non-cross over, was conducted in healthy, non-pregnant, non-lactating women volunteers at 60 and 120 mg doses along with identical placebo tablets given daily per oral for 30 days. The compound was well tolerated and there were no adverse effects in clinical and laboratory parameters in both the studies (7,8,15).

5.2. Dose ranging studies in women for contraceptive efficacy

5.2.1. Post-coital schedule

The contraceptive efficacy trial with Centchroman in the 60 mg post-coital schedule included 103 women of reproductive age group. Pregnancy protection was within acceptable limits; one method failure (MF) and two patient failure (PF) pregnancies occurred within the first three months. Average use of Centchroman by subjects in this schedule ranged from 15- 40 tablets per month, one tablet after each coital act. About 13% menstrual cycles were delayed by more than 15 days and cycles showed normal pattern after drug discontinuation (7,8,16) with no other side effects or complaints.

5.2.2. Once-a-week schedule

The terminal half-life of Centchroman is about 168 hours and thus the drug intake by users in the post-coital schedule averaged around 25 tablets per month due to repeated acts. Accordingly, the dose ranging studies were undertaken in the once-a-week schedule at doses tapered from 120 mg to 10 mg per woman per week. Women volunteers in the reproductive age group belonging to different socio-economic status and less than 30 years of age having one living child participated. More than 100 volunteers at each dose had drug use duration for at least 5 cycles. The contraceptive efficacy and side effects at each dose were assessed before taking up the next dose except that trials at 15 and 10 mg doses were conducted concurrently. A total of about 1, 000 volunteers have been covered for nearly 7, 000 months of use. Centchroman at 30 mg weekly dose showed best contraceptive efficacy with no side effects except about 8% delayed menstrual cycles. The menstrual delay was seen at all the doses, was random and not confined to any particular cycle or individual or centre. The women showing delayed cycles resumed normal cycles while continuing drug use. No other side effects were observed or complaints reported (7,8,16).

5.3. Phase III multicentric trial

5.3.1. 30 mg Once a week schedule

A total of 909 women volunteers of reproductive age with 1 or two living children in 5 Family Welfare Centres in Lucknow and seven Medical Colleges in the State of Uttar Pradesh participated in the 30 mg once a week dose schedule trial. The volunteers were enrolled in the year 1981 and the trial initiated in 1982. These volunteers have been covered for use duration of 12, 828 months and 11, 448 cycles with acceptable pregnancy protection (Pearl Index: 3.76). Pregnancy protection in all the trials was within acceptable limits with Pearl Index varying at from 1.20 – 4.20 with an average of 2.79. No side effects were observed or reported except that about 8.84% of the menstrual cycles were longer than 45 days, though most of the subjects resumed normal cycle while continuing use of Centchroman. “A mid-term life-table analysis of the trial data of 368 subjects for 3658 months of use with 12 MF pregnancies by ICMR showed that 30 mg weekly dose of Centchroman produces minimal side effects and has desired efficacy (pregnancy rate at 12 months is 4.09 by 100 users); P.I. 4.4 per 100 women years. Data on menstrual cycle length indicates good cycle control. Discontinuations due to delay or menstrual abnormalities and other medical reasons were observed to be minimal as compared to any other hormonal contraceptive. However, the pattern of menstrual delay is random and not confined to any cycle or individual”. If data of 30 mg confirmatory dose is included, a total of 992 women volunteers received 30 mg weekly dose of Centchroman for 13, 965 months of use with good pregnancy protection (P.I. 2.84). Considering 30 mg and higher weekly doses, a total of 1, 651 women volunteers used Centchroman for 19, 863 months of use with P.I. of 2.78 and that is excellent pregnancy protection. The only side effect reported so far has been delay in about 8% menstrual cycles (7,8,17,18).

5.3.2. 30 mg Biweekly cum 30 mg weekly schedule

The pregnancy protection in the 30 mg weekly schedule was within the acceptable limits but most of the pregnancies which occurred were within the first three months of drug use. It is well known that it takes about 5 to 6 half-lives (Centchroman terminal half-life is ~168 hours) to reach steady state levels in the body and therefore a study of 30 mg biweekly dosing given at the beginning for 12 weeks followed by 30 mg weekly schedule thereafter was undertaken.

This multicentre trial with Centchroman at the 30 mg biweekly cum weekly dose schedule was conducted at five Family Welfare Centres in Lucknow and seven State Medical Colleges in Uttar Pradesh. Each women participant took the first 30 mg dose biweekly (twice-a-week) beginning on first day of menses and thereafter every Wednesday or Sunday, whichever day came first after initiating Centchroman use, for three months followed by weekly dose (Wednesday or Sunday) from 13th week onwards for as long as contraception is desired. Three hundred and seventy seven (377) women volunteers of proven fertility with 1 or 2 living children with normal menstrual cycle pattern and gynaecological history participated in this schedule trial. They were covered for a total of 3, 932 months and 3, 471 cycles of use with acceptable pregnancy protection (P.I.: 1.83). The cumulative pregnancy protection by life table analysis at 12 months is 1.63 ± 0.74. In this dose schedule, only

3.7% of the menstrual cycles were delayed beyond 45 days and the pattern of menstrual delay, as reported earlier, is random and not confined to any particular cycle or individual or centre (7,8,19).

An assessment of the Phase II/III clinical trials in over 2, 000 women volunteers of reproductive age and covered for about 25, 000 months of use clearly shows that there is acceptable pregnancy protection with Centchroman at 30 mg weekly or higher doses and 30 mg biweekly cum weekly dose schedule (7). The 30 mg biweekly cum weekly dose schedule gave better pregnancy protection and cycle control and therefore has been recommended for wider clinical use with DCGI permission.

The clinical observations, laboratory investigations including organ function tests and ultrasonography, reversibility of fertility and effect on progeny includes subjects of 30 mg weekly and 30 biweekly-cum-weekly dose schedules were also carried out.

5.3.3. Clinical observations

All the volunteers were healthy at recruitment and none of them reported any drug related side effects or were observed at regular clinical checkups. The only side effect reported was a delayed cycle of more than 45 days in about 8% menstrual cycles at 30 mg weekly dose schedule and in about 3.7% cycles in biweekly cum weekly dose schedule. The delay in both dose schedules was random and not confined to any cycle or individual. The delayed menstrual cycles didn't bother subjects with good counseling and assurance of not-pregnant. The delayed menstrual cycles returned to normal pattern in most of the women with continued Centchroman use, however in some cases the drug was temporarily withdrawn to normalize cycles. Pertinently, none of the subjects reported flushing, nausea, vomiting, dizziness, weight gain, breakthrough bleeding or change in cholesterol and platelet functions commonly seen with steroidal oral contraceptives (7,8,17–19).

5.3.4. Clinical chemistry

About 25% (377) of women volunteers underwent thorough blood chemistry, haematology and organ function tests. Nothing abnormal was diagnosed and all the findings were within normal limits. The findings on 122 women volunteers with Centchroman use of 1–4 years and 40 age-matched controls clearly showed that the drug had no adverse effect on cholesterol, triglycerides and HDL cholesterol and did not cause aggregation of platelets. The levels of FSH, LH, F2 and PG were tested in 40 women who had used Centchroman for 12–24 months and values were within normal limits (7,8,17–19).

5.3.5. Ultrasonography of genital organs

Nothing abnormal was detected in per vaginal examination of ovaries, cervix and uterus. Ultrasonography was conducted in 175 women volunteers at different time intervals and in some cases sequentially at 0, 3, 6, 9 and12 months of Centchroman use; the size of the ovaries and uterus remained within normal limits. However, enlargement of the ovary was observed in about 15% of both the Centchroman treated and controls or placebo users and was found to be due to unruptured follicle which disappeared in subsequent cycles and thus appeared to be a normal incidence in women of reproductive age; the utero-ovarian ratio then was within the normal range. Twelve cases of 29–52 months of Centchroman use underwent laparoscopic examination of ovaries which were found to be normal (7,8,20).

5.3.6. Reversibility of fertility

Fifty seven women with 1 or 2 living children withdrew from the trial to have another child. All of them had uneventful pregnancy, 40 conceived within 6 months, another 13 within 12 months and 4 after 12 months of discontinuing the drug. And one more woman with 5 living children also left using the drug and she did not become pregnant probably didn't want another child (7,8,17–19).

5.3.7. Effect on progeny

All the user failures (64) and reversal group (57) women had uneventful pregnancy and gave birth to healthy babies. 117 babies were followed for at least one year and presented normal development milestones. Forty eight of these children of different ages and sex have been followed for almost 11 years and had normal physical, social and mental milestones (7,8,17–19).

6. CENTCHROMAN: DEVELOPMENT KINETICS AS AN ORAL CONTRACEPTIVE

The milestones in the development of the Centchroman are included in Table 1. It may be mentioned that at each step beginning with the preclinical development along with protocol for the next study was submitted to the Drugs Controller General of India and after his approval the next study was initiated. Each approval took 4 to 6 months and the marketing permission took around one year. It is pertinent to add that the DCGI was very considerate and got the data of each phase evaluated on priority.

The MOH&FW supported and closely monitored the development of Centchroman from beginning i.e. 1968 and took it up for its Social

Table 1. Milestones and dates for development of Centchroman

Landmark milestones	Dates
Design and synthesis of chroman CDRI 67/20	Jan 1967
Identification of the compound 67/20 as a potential oral contraceptive by testing in rodents, dogs and monkeys	1 year (1968)
Preclinical development including regulatory animal toxicity studies	2 ½ years (1970)
Centchroman brand name accorded to the Chroman contraceptive from Central Drug Research Institute	1971
Phase I Clinical Trial – Human safety studies	1 year (1972)
6-Months toxicity in rats and rhesus monkeys, mutagenicity and life-time carcinogenicity in mice and rats during dose ranging studies Phase IIA Clinical Trial: Proof of concept and dose ranging studies	5 years (1977)
Phase IIB Clinical Trial: Dose confirmation study	6 years (1983)
Phase III Multicenter clinical trial: 30 mg weekly dose	4 years (1987)
30 mg Biweekly for 3 months followed by 30 mg weekly from 13th month for as long as contraception is desired	2 years (1989)
Approval by DCGI for marketing as post-coital/weekly contraceptive pill	1 year (Nov 1990)
Licensed to Hindustan Latex Ltd now HLL Life Care Ltd	1991
Thiruvananthapuram and Torrent pharmaceuticals Ltd, Ahmedabad HLL Life Care marketed Centchroman as a biweekly-cum-weekly pill under the trade name **"Saheli"**	1991-present

Marketing Programme in 1995, after reviewing the Post-Marketing Surveillance data of about 100,000 women for 1100, 000 menstrual cycles. It has now been decided to include Centchroman in National Family Planning Programme under the trade name "**Chhaya**" from April 2016. It will be the first contraceptive used in the National Family Welfare Programme discovered and developed in India, and perhaps the **first non-steroidal contraceptive in use in the world.**

7. CENTCHROMAN AS A SERM: OTHER CLINICAL USES

7.1. Estrogen antagonist

7.1.1. Control of dysfunctional uterine bleeding (DUB)

The major side effect observed with Centchroman is a delay in menses in some women. During the clinical trials of Centchroman as a contraceptive, Prof. Raj Baveja at the Kamla Nehru Hospital and Medical College at Allahabad, in an exploratory study, observed the beneficial effects of Centchroman in the control of DUB and menorrhagia which appeared to be related to the side effect of delay in menses reported in Centchroman trial. Following this observation, Torrent Pharma, Ahmedabad carried out Regulated Clinical trials on the management of DUB and Menorrhagia with Centchroman and confirmed this finding and got the approval of DCGI in 1995 for marketing. Centchroman was licensed for marketing to Torrent under the trade name "**Sevista**" and to Hindustan Latex and Life Care Ltd under the trade name "**Novex-DS**". Soon, publications started appearing highlighting the beneficial features of Centchroman for the management and control of DUB and menorrhagia. An investigator conducted a study at a dose of 30 mg twice weekly for 6 months in 70 women suffering from menorrhagia and the reduction in blood loss was 80 to 87.78% (21). In another study, eighty five women with complaints of DUB were treated with Centchroman (Sevista) at a dose of 60 mg twice weekly for first 3 months followed by 60 mg weekly for next 3 months. The reduction in menstrual blood loss as measured by pictorial blood loss chart score (PBAC) was 97.2%. Seventy four patients (87.05%) showed significant reduction in endometrium thickness as assessed by trans-vaginal sonography. "The convenient dosage schedule and high cost benefit ratio makes it a drug of choice for menorrhagia" (22,23). Gynaecologists at the All India Institute of Medical Sciences, New Delhi also determined the efficacy of Centchroman in the management of dysfunctional uterine bleeding. The effect of 60 mg biweekly dose for 3 months followed by 60 mg weekly dose for one month was studied in 42 women with menorrhagia. The menstrual blood loss was measure by PBAC and by visual analog scale (VAS). The overall response rate as assessed by pain and percentage reduction in blood loss was 97.7% at 4 months (24). A double blind controlled comparative study of Centchroman and medroxy progesterone acetate (MPA) was conducted in 84 women, 42 on each drug. Centchroman was given at a dose of 60 mg twice a week (3 days apart) while MPA at a dose of 10 mg for 21 days in each cycle, both drugs were given for 3 consecutive cycles for the management of DUB. The response rate with Centchroman (85.71%) was much better than that with MPA (54.76%); the endometrial thickness reduction was more with Centchroman (25). In another study in the same schedule, there was significant improvement in 84% patients suffering from dysmennohorea along with significant reduction in endometrial thickness (26). Another study reported 88.3% reduction in

blood loss by PBAC score and more than 1.8% gm gain in haemoglobin and reduction in endometrial thickness as recorded at 6 months (27). Shahab *et al* conducted a comparative study of Centchroman and Norethisterone in 300 patients of DUB, 150 patients with each drug. Centchroman was administered at a dose of 60 mg twice weekly for 3 months followed by 60 mg weekly for another 3 months whereas Norethisterone was given at dose of 5 mg twice a day continuously, 12 days in every cycle, for 6 months. 123 Women (82%) in Centchroman group and 45 (30%) in Norethisterone group showed marked improvement of symptoms with significant reduction in blood clots and regression of PBAC score. Centchroman group showed better compliance and acceptability with marked relief in symptoms; significantly less number of women in this group had to undergo hysterectomy (28). The next study used a dose of 60 mg twice a week for 3 months followed by once a week for 6 months and was conducted in 50 women suffering from menorrhagia; the response rate was 87.5% by PBAC (29). In all the studies there was gain of more than 1% in haemoglobin.

7.1.2. Control of mastalgia (breast pain) and fibroadenoma

Centchroman (ormeloxifene) has been studied for the treatment of benign breast disease by a number of investigators. The first study included 42 patients with mastalgia with or without nodules and 18 patients of fibroadenoma. 38 Patients reported non-cyclical pain and 4 had cyclical pain. 38 Patients had visual analogous scale (VAS) score 10 with severe pain and 9 had VAS score 7–10. Fibroadenoma size ranged from 1.5–5.0 cm, single or multiple in one or both breasts. Centchroman was given at a dose of 30 mg every other day for 3 months and patients were followed for 6 months. The mastalgia group showed good response with VAS score reduced from 10 to 3 in 90% of the patients in the first week of treatment. All patients were painless after one month and there was total disappearance of nodularity. There was complete disappearance of fibroadenoma in 40% patients, partial response in 20% and no response in 40%. The studies shows that it is a safe drug showing very good response in mastalgia as compared to drugs of choice used currently (Danazol and Bromocriptine) and had very few side effects (30). In another study, Centchroman versus Danazol was evaluated for the management of mastalgia in 81 patients; 42 on Centchroman (30 mg daily) and 39 on Danazol (100 mg daily), the drugs were given daily for 3 months and evaluated at 1, 4, 8, 12 and 24 weeks after stopping the drugs. At 12 weeks after stopping the drugs, the reduction in pain (VAS score) was in 89.7% patients in Centchroman group and in 67.94% patients in Danazol group; Centchroman was more effective than Danazol in pain reduction even at 24 weeks. The reduction in nodularity and breast tenderness was seen in 100% patients on Centchroman and in 90% on Danazol. No other side effects except for delay in menses were observed with both the drugs (31). A double blind placebo controlled study with Centchroman was conducted for the treatment of breast pain and nodularity in 121 patients. Centchroman or placebo tablets were given twice a week for 12 weeks; pain was assessed by VAS score and nodularity by Lucknow-Cardiff scale. The pain was significantly reduced in the drug treated group from 5th week onwards. Grade 2 or lower nodularity was **s**een in 93.3% patients as compared to 72.1% in placebo group. The only side effect was oligomenorrhoea in 12 patients (32). In another study, 203 patients suffering from mastalgia and fibrocystic breast disease were treated with Centchroman at a dose of 30 mg on alternate days for 3 months. The main pain level continuously decreased over 5 visits (5.8 to 0.86); 30.6% of patients at 5th visit had grade 1 or 2 nodularity which was observed in 92.6% patients at the end of 6 months (33). The curative effect of Centchroman on mastalgia and fibroadenoma has been reported by four independent groups involving 465 patients with response rate of more than 90% and also found to be better than Danazol, the drug of choice for these disorders (30–33).

7.1.3. Centchroman (Ormeloxifene) for reproductive organ cancers

7.1.3.1. Breast cancer

Eighty nine patients (82 females and 7 males) suffering from advanced cancer of breast (stage III/IV), and rejects to all modalities of therapy were treated with Centchroman at an oral dose of 60 mg thrice weekly for 4–6 weeks and thereafter to responders until relapse. Results were evaluable in 79 (75 female and 4 male) who completed therapy. Thirty eight patients reported relief of pain; of these 10 were complete responders, 22 partial and 6 non-responders. An overall response was observed in 38.7% percent female patients and the median duration of response in responders was 6 months (2–18 Months). The response was better in peri- and post-menopausal groups; however there was no correlation between response rate, number of lesions and estrogen receptor (ER) status. The response was better in skin, soft tissue, lymph nodes and skeletal lesions. In 4 male patients, one showed complete response with complete disappearance of soft tissue and nodal metastases, two had partial response and one did not respond, the response matched with ER status**.** Centchroman had no effect on haematology, renal, hepatic and pancreatic functions. The response rate in female patients is comparable to tamoxifen (34). The multicentric trial was conducted in advanced cancer of breast in six hospitals. Positive response was seen in 52% patients which is better than tamoxifene, the drug currently used (CDRI unpublished).

7.1.3.2. Ovarian cancer

In preliminary studies, Centchroman (ormeloxifene) has shown potent anti-neoplastic activity in ER positive breast cancer cell lines and has also shown genotoxic activity against primary ovarian cancer cells taken from patients (35). In *in vitro*, Centchroman has been found to inhibit cell growth and induce apoptosis in ovarian cancer cell lines including Cisplatin-resistant cell lines. Further Centchroman has been shown to markedly inhibit tumorigenesis and metastasis in xengraphts in mouse (36).

7.1.3.3. Prostate cancer

Recent studies suggest that Centchroman (ormeloxifene) stimulates certain key oncogenic pathways to inhibit growth of prostate cancer cells. Preliminary studies with Centchroman have also shown inhibition of growth of androgen independent and dependent prostate cancer cells via induced apoptosis (35).

7.1.4. Centchroman (Ormeloxifene) for other cancers

7.1.4.1. Head and neck cancer

Centchroman (ormeloxifene) has also been shown to inhibit growth of head and neck cancer cells (HNSC) by inducing apoptotic cell death through the activation of Caspase 3. The drug treatment inhibits the phosphorylation of AKT and thereby promotes downstream AKT signaling. This in turn stops cell cycle, inhibits cell proliferation, survival and enhances apoptosis (35).

7.1.4.2. Pancreatic cancer

Centchroman (ormeloxifene) treatment has been shown to deplete tumour associated stromal tissue by inhibiting the paracrine sonic hedgehog signaling pathway in pancreatic ductal adenocarcinoma (PDAC). Its effect on cell proliferation and apoptosis was also studied in comparison with Gemcitabine, the drug currently used in such cancers. Centchroman has been found to significantly stimulate (by ~ 75%) the effect of Gemcitabine in PDAC xenographt mice. Further it also reduced tumour associated stroma in xenographt tumour tissues and inhibited stromal cell infiltration into tumour tissue. Centchroman treatment also inhibited the invasiveness of tumour cells co-cultivated with TGFβ-stimulated human pancreatic tissue *per se* or conjointly with Gemcitabine. The investigators suggest that Centchroman along with Gemcitabine may be the therapy of choice in PDAC/ pancreatic cancer (37).

7.1.4.3. Chronic myeloid leukemia

. Centchroman (ormeloxifene) is reported to induce concentration dependent increase in apoptosis of multiple CMS cell lines by arresting at the growth phase and inducing ERK mediated apoptosis. The best effect is seen in 562 CML cell lines (35).

7.2. Estrogen agonist

7.2.1. Centchroman (ormeloxifene) for the management of osteoporosis

Osteoporosis occurs mainly in post-menopausal women when the ovary secretes estrogen in lower quantities. A random double blind placebo controlled study with levo-Centchroman (levormeloxifene) at single ascending doses from 2.5 to 320 (6 doses, 8 subjects at each dose and 2 on placebo; 6 active at each dose and 2 placebo),) and four multiple doses ranging from 20 to 160 mg (16 subjects at each dose and 4 on placebo; 12 subjects active at each dose and 4 placebo), each dose once daily, was conducted in 104 post-menopausal women. After 5 weeks of treatment with 20 to 160 mg doses and thereafter for 8 weeks with 40 or 80 mg, the biochemical marker of bone turnover, I C-terminal telopeptide, was significantly reduced; however the reduction was not dose dependent. The drug was well tolerated and the side effects included headache, abdominal pain and leukorrhea more so with the highest multiple dosing of 160 mg. The study suggested estrogen like bone preserving effect of levo-Centchroman (38,39). Phase II clinical trial with levo-Centchroman for the treatment of post-menopausal osteoporosis was conducted in Scandinavia in 300 women at a high dose. After 12 month therapy, the bone mineral density of the lumber spine was increased by 2.5–3% as compared to placebo. Uterine endometrial thickness probably due to fluid retention was seen. Accordingly, a Phase III trial in 4,000 elderly (post-menopausal) women at a lower dose was initiated. Endometrial thickening (as detected by ultrasound) in about 40% women due to fluid retention was observed; however, there was no evidence of proliferation or hyperplasia. Higher incidence of urinary incontinence and utero-vaginal prolapse as compared to normal rate was also noticed. The drug did not cause breast tenderness as seen with hormone replacement therapy and other drugs and a showed a positive effect on vaginal atrophy. The drug showed a positive effect on bone density (39,40). A 12- month double blind study to understand the effect of levo-Centchroman (levormeloxifene, 1.25, 5, 10 or 20 mg/ day), HRT (Norethisterone acetate and estradiol-17β) or placebo given continuously for one year on bone loss in post-menopausal women was conducted;

50 women in each group. All women were given daily calcium supplement (500 mg). Levo-Centchroman had a positive effect on bone mineral density and bone turn over. Endometrial thickness was seen at all the doses with levo-Centchroman. Hot flushes in levo-Centchroman groups were similar to HRT but were more with HRT. Breast tenderness was more common in HRT group than in all other groups(41).

7.2.2. Centchroman (Ormeloxifene) and its levo isomer for cardioprotective effects

Lipid profile studies done during the multicentric trial on 122 women volunteers with Centchroman use of 1–4 years and 40 age-matched controls clearly showed that the drug had no adverse effect on cholesterol, triglycerides and HDL cholesterol and did not cause aggregation of platelets indicating cardiovascular protective effects (7,8,17–19). Phase II double blind placebo controlled clinical trial with levo-Centchroman to study the effect on bone turn over and lipid profile was undertaken at doses of 20 to 160 mg given for 5 weeks. The drug had a favourable cardiovascular profile with a significant decrease in serum total (15%) and LDL-cholesterol (25%), without affecting triglyceride or HDL-cholesterol levels, indicating antiatherogenic effect on the cardiovascular system; however, the effect was similar at all the doses. In another parallel study, levo-Centchroman was given at doses of 40 or 80 mg/day to 24 post-menopausal women (12 at each dose) for 56 days. The results were virtually similar to the double blind group (40). The plasma fibrin was reduced by 15% and none of the parameters indicated any increased incidence of deep vein thrombosis (39–41). A 12- month double blind study to understand the effect of levo-Centchroman (levormeloxifene, 1.25, 5, 10 or 20 mg/day), HRT (Norethisterone acetate and estradiol-17β) or placebo given continuously for one year on lipid profile in post-menopausal women was conducted; 50 women in each group. All women were given daily calcium supplement (500 mg). Levo-Centchroman had significantly decreased low density lipoprotein cholesterol by about 22–30% as compared to 12% with HRT but high density lipoprotein cholesterol was unaffected (41). Another study showed that Centchroman (ormeloxifene) and levo-Centchroman (levormeloxifene) do not show thrombin inhibitory activity but raloxifene showed thrombin modulatory effect and which may be the cause of thromboembolic complications seen with this drug. Thus Centchroman and levo-Centchroman seem to have positive effect on cardiovascular system (42).

8. MARKETING

Centchroman is marketed under the trade name "**Saheli**" as a biweekly-cum-weekly oral contraceptive by HLL Life Care Ltd and it has been included in the National Family Welfare Programme by the MOH&FW from April, 2016. HLL Life Care Ltd is also marketing Centchroman for the management of dysfunctional uterine bleeding under the trade name '**Novex-DS**" and Torrent Pharmaceutical Ltd as "**Sevista**".

9. SERMs IN CLINICAL USE

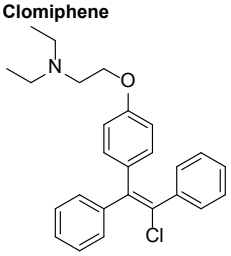
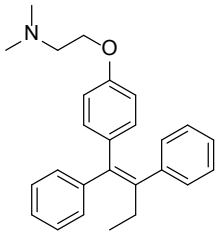
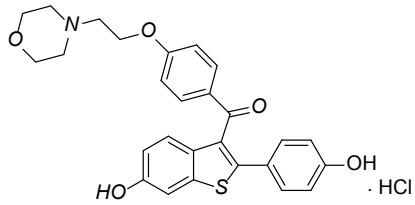
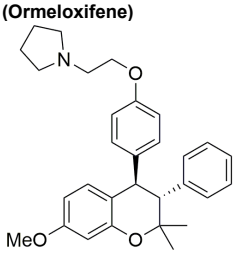
Selective estrogen receptor modulators are those compounds which show estrogen agonist property in some tissues and estrogen antagonist activity in others. The first estrogen antagonist synthesized was MER-25 in 1958. Some authors say that it is not a SERM whereas others say that being a silent estrogen agonist and potent antiestrogen i.e. estrogen antagonist it may be considered as SERM. Centchroman has also been found to be a SERM as it shows estrogen agonist activity in bone, cardiovascular system and estrogen antagonistic activity in DUB, breast and associated cancers, ovary, prostate and other cancers.

The preclinical and clinical profile of some of the clinically used SERMs, namely clomiphene, tamoxifene, raloxifene and Centchroman (ormeloxifene), is given in a Table 2.

10. ACKNOWLEDGEMENT

The authors express sincere thanks to all the Directors of CDRI for their keen interest and support, Staff of CDRI, Clinicians and Volunteers who participated in the preclinical development studies and clinical trials, Coordination Committee for the clinical trials, UP State Family Welfare Dept. for all the support and well-wishers and friends of CDRI. The authors express sincere gratitude to MOH&FW, Govt. of India which supported CDRI since 1968 for its Family Welfare efforts as also supporting and monitoring the Centchroman clinical trial and ICMR for mid-term analysis of the data. The Ministry also involved its HLL Life Care Unit to successfully market Centchroman. We sincerely thank Dr. M. Ayyappan, CMD, of HLL Life Care in taking keen interest in marketing this drug as a contraceptive and for the management of dysfunctional uterine bleeding and Torrent Pharmaceuticals for supporting and marketing it for dysfunctional uterine bleeding. The authors record their gratitude to late Dr. A. B. Kar and late Dr. Swaran Nityanand, both of CDRI who played key roles in different facets of Centchroman development. Dr. Kar was one of the initiators of this programme at CDRI and led the preclinical contraceptive development studies and Dr. Swaran Nityanand meticulously monitored the clinical trials.

Table 2. SERMs in clinical use

Compositions			
Clomiphene  Triphenylethylene	**Tamoxifene**  Triphenylethylene	**Raloxifene**  Benzophenone	**Centchroman (Ormeloxifene)**  Triphenylethane
Biological Profile			
Estrogen agonist in some tissues and antagonist in others Estrogen antagonist on hypothalamus to release Gn and then FSH & LH from pituitary Estrogen agonist on bone and CVS No progestational, androgenic or antiandrogenic effect No effect on adrenal or thyroid functions	Moderate estrogen and potent antiestrogen in rat uterus Estrogen agonist on bone and CVS Inhibits MCF-7 human mammary cells *in vitro*	Little estrogen and potent antiestrogen in rat uterus Estrogen agonist on bone and CVS Inhibits MCF-7 human mammary cells *in vitro*	Weak estrogen and potent antiestrogen in rat uterus No effect on hypothalamus-pituitary-gonad axis Estrogen agonist on bone and CVS No progestational, antiprogestational, androgenic or antiandrogenic effect No effect on adrenal or thyroid functions Inhibits MCF-7 human mammary and other cancer cells *in vitro*
Regulatory Toxicity			
Safe	Affects liver, teratogen, carcinogen	Reproductive, teratogenic and carcinogenic hazard	Safe
Therapeutic Index			
Excellent	Narrow	Excellent	Excellent
Clinical Use			
Used in sub-fertility and polycystic ovarian syndrome	Used in metastatic breast cancer	Used in post-menopausal osteoporosis, may be prophylactic in breast cancer and CVS	Used as oral contraceptive, cure of DUB, mastalgia & fibroadenoma, indicated for breast cancer, prophylactic in osteoporosis and CVS
Clinical Side Effects			
Common: Hot flushes, pelvic pain :Less frequent- Vomiting, trouble in sleeping, ovarian cancer, changes in vision	Common: Amenorrhoea, fluid retention, hot flushes, vaginal discharge/ hemorrhage, weight loss, : Less frequent- Increased risk of uterine cancer, stroke, vision problem, pulmonary embolism	Common: Hot flushes, leg crumps Risk of blood clots, sudden vision changes, breathing confusion, headache, dizziness, nausea, vomiting, joint pain	Delayed menstruation in about 8% menstrual cycles

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Key Words: Centchroman, Ormeloxifene, INN, Oral Contraceptive, Dysfunctional Uterine Bleeding, Breast and Associated Cancers, Osteoporosis, Review

Send correspondence to: Ved P. Kamboj, Central Drug Research Institute, Lucknow, India, Tel: 91-522-2771941/2344333, Fax: 91-522-2771941, E-mail: kambojvpk1511@gmail.com